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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/744,110	12/06/96	CHEN	Y

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EXAMINER	
BERCH, M	

ART UNIT	PAPER NUMBER
1611	5

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/764,110	Applicant(s) Chen
	Examiner Mark L. Berch	Group Art Unit 1611

☒ Responsive to communication(s) filed on *1/30/98*

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *2-5, 8-10, 12-14, and 18-21* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *2-5, 8-10, 12-14, 18, 20, and 21* is/are rejected.

☒ Claim(s) *19* is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Claims 20-21 are rejected, 35 USC 112, paragraph 1, for lack of enablement for such scope. The reasons were given previously; the traverse on this point is unpersuasive.

No medicinal even known to man has ever been capable of treating such a staggering scope of disorders. To get a single compound, let alone a genus of billions, to be effective against such a vast array of disorders has been beyond the reach of medicine. The failure to achieve such a goal in the past places the burden on applicants to show that their compounds really can accomplish this, for reasons set forth previously, including the citation of case law. It is allegedly effective against a huge variety of psychological disorders (e.g. recurrent and much more), inflammatory disorders (e.g. allergies), a variety of neurodegenerative disorders (e.g. AD), all chemical dependencies regardless of type, CNS disorders (Stroke) and developmental disorders (dwarfism). It is claimed to be used in good number of the body's basic systems, such as cardiovascular (hypertension, tachycardia), gastrointestinal (IBS, spastic colon, ulcers), joints (rheumatoid arthritis), immune (immune suppression), muscular (muscular spasms), excretory (urinary incontinence) etc. It is effective against disorders normally thought of a untreatable, such as mutiinfarct dementia. Applicants' genus of billions of compounds has such a wide range of action as to be a general panacea. However, such a generalized panacea is not deemed enabled, *In re Citron*, 129 USPQ 520.

This is particularly true for something like cancer. The claim sets forth the treatment of cancer <u>generally</u>. However, there never has been a compound capable of

treating cancer generally. Applicants argue that there are compounds that treat a range of cancers. This is true, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. Despite the understanding, as applicants state, that chemotherapeutic agents destroy malignant cells without substantially interfering with the growth of normal cells, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Much the same is true, for example, for "chemical dependencies and addictions". The notion that a compound could be effective against chemical dependencies in general is absolutely contrary to our current understanding of how chemical dependencies operate. There is not, and probably never will be, a pharmacological treatment for "drug addiction" generally. That is because "drug addiction" is not a single disease or cluster of related disorders, but in fact, a collection with relatively little in common. Addiction to barbiturates, alcohol, cocaine, opiates, amphetamines, benzodiazepines, nicotine, etc all involve different parts of the CNS system; different receptors in the body. For example, cocaine binds at the dopamine reuptake transmitter. Heroin addiction, for example, arises from binding at the opiate receptors, cigarette addiction from some interaction at the nicotinic acid receptors, many tranquilizers involve the benzodiazepine receptor, alcohol involves yet another system, etc. All attempts to find an pharmaceutical to treat chemical addictions generally have thus failed.

Applicants list AIDS. All successful treatments of AIDS have involved antiviral agents. No one has ever been able to get other attempts to work. This shows that the skill level in this art is not high enough to get other methods to work. Similarly with the treatment of AD. Getting agents to be effective against AD has proven extremely difficult. Despite extraordinary efforts with a variety of agents in this area, only two pharmaceuticals have been made to work, both acetylcholinesterase antagonists, a property that these compounds are not disclosed to have. No one has been able to figure out how to get CRF regulators to be effective against AD, which is evidence of the low skill level in this art relative to the difficulty of the task.

To further rebut applicants' arguments, Chalmers is cited as an example of the skill level in this art as of 1996. Note especially pages 171-172, which deal with "Therapeutic Strategies". Three things are of particular relevance:

1. AD and eating disorders, including obesity and anorexia nervosa are associated with abnormally low levels of CRF. Therefore, administration of CFR antagonists, if they had any effect, would be expected to make matters worse.

2. Stroke appears in the claim. Chalmers says (page 170) that "there are no effective neuroprotective agents that can clinically ameliorate the effect of stroke in humans." This is evidence that, despite decades of effort to treat stroke, that the skill level in the art is just too low relative to the task to figure how to get a pharmaceutical to do this.

3. The full paragraph on page 171 lists several general strategies for high-CRF disorders. It is clear from the wording, however, that as of 1996, it had not been determined

to how or even whether this proposed strategy was going to be made to work. The paragraph speaks about possible progress in the future, such as how to target the drug to a particular tissue or region. Progress is talked about as coming in the future, to "provide potential treatment for a number of disease states." The article makes no mention at all of anyone having figured out as of 1996 how to actually do this. The concluding remarks on page 172 state explicitly that it is "future investigation of multiple CRF subtypes [a consideration of which doesn't even appear in this specification] ... will also provide a basis for rational drug design for the treatment of disease states that are associated with abnormal CRF levels." This is clear evidence that as of 1996, such a utility was not enabled.

A second piece of evidence is the Stratakis reference, showing state of the art in 1997. In 6 pages of discussion of CRF, there is only a single sentence devoted to use of CRF antagonists. It is clear from the wording that such efficacy is in the future --- these "might prove useful". Also note that the following sentence adds atypical depression, chronic fatigue/fibromyalgia and autoimmune disorders to the list of disorders which have CRF levels too low, which CFR antagonists would be expected, if anything , to make worse.

Claims 20-21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

1.Replacement of the "previous HIV infections" with "AIDS" is clearly new matter. These are not the same thing. One occurs years after the other.

2.Deletion of "psychosocial" from before "dwarfism" clearly broadens the term, since now it covers any type of dwarfism.

Claims 20-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term (a) language is vague. Applicants have not come to terms with the problems set forth in point 7a. Determining whether a given disease responds or does not respond to such antagonism will surely involve undue experimentation. Suppose that a given CRF Antagonist X when administered to a patient with Disease D does not obtain a response. Does one then conclude that Disease D does not fall within this claim? Keep in mind that:

A. It may be that the next patient will respond. It is quite common for pharmaceuticals to work only with some people, not all. Thus, how many need to be tested?

B. It may be that the wrong dosage or dosage regimen was employed. It is quite common for pharmaceuticals to work at one dosage, but not at another which is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? Thus, how many dosages

and dosage regimens must be tried before one is certain that this pharmaceutical won't affect Disease D?

C. It may be that X simply isn't potent enough for Disease D, but that another antagonist Y is potent enough, so that D really does fall within the claim. Thus, how many different antagonists must be tried before one concludes that D doesn't fall within the claim?

D. Conversely, if D responds to Y but not to X, can one really conclude that D falls within the claim? It may be that the X result is giving the accurate answer, and that the success of Y arises from some other unknown property which Y is capable of. Thus, when mixed results are obtained, how many more pharmaceuticals need be tested?

E. Finally, suppose that X really will work, but only when combined with Z. There are for example, agents in the antiviral and anticancer technology which are not themselves effective, but the disease will respond when the agents are combined with something else.

F. In addition, literally speaking, any disorder can be treated with any drug, although the treatment might not be successful. Assuming that "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000?

As a result, determining the true scope of the claim will involve extensive and potentially open-ended research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Claims 2-5, 8-10, 12-14, 18, 20-21 are rejected under 35 U.S.C. 112, paragraphs 1 and 2, as the claimed invention is not described, or is not described in such full, clear, and exact terms as to enable any person skilled in the art to make and use the same, and/or failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. Specifically:

1. The revised R^1 language of having single bonds in C_1-C_4 alkyl groups "replaced by" double or triple bonds is clearly erroneous and hence could not have been the original intention. A C_1 alkyl group has no "carbon-carbon single bond" to replace. The same is true in R^2 and in R^5 (see point 3 below).

2. The replacement of the term "thioalkyl" with "alkylthio" is clearly new matter. There is no way of telling whether that term or "mercaptoalkyl" is what was originally intended; applicants have simply made a determination after the filing date. Although the original terms was clearly defective, both "alkylthio"and "mercaptoalkyl" are reasonable possibilities as to what was originally intended. Applicants' reasoning that it could not have been "S-alkyl" since that terms is impossible, and therefore it must be "alkylthio" ignores the "mercaptoalkyl" choice.

3. Original point 6 remains. Even with the new material added to Claim 1 (discussed in point 4) and into the specification (see objection below), the claim 3 material is still broader. First, it covers R^5 as Pyridyl and pyrimidinyl, which for some reason isn't in the additional material added. Second, the additional material covers only alkyl groups,

whereas Claim 3 also covers the C_1-C_4 alkyl in alkoxy, alkoxyalkyl, and hydroxyalkyl groups (see page 51, lines 28-29).

4. The addition to the R^5 definition, while described (in original claim 3), lacks utility for the reasons set forth in the objection to the specification.

5. Claim 5 now does not further limit; the claim is superfluous.

The specification is objected to because of the addition of material to page 4. This material, although described in original claim 3, had no teaching of how to use attached to it. Its present place, as part of the definition of Formula I, places this subject matter under the specification's teaching of how to use. Hence, it is new matter to ascribe to this material a teaching of how to use. Deletion is required.

Claims 2-5, 8-10, 12-14, 18, 20 and 21 are rejected as being drawn to an improper Markush groups for reasons set forth previously. Limiting the claims to pyrrolopyrimidines will overcome the rejection.

Claim 19 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Mark Berch whose telephone number is 703-308-4718.

Mark L. Berch

Primary Examiner

Group 1600 - Art Unit 1611